CIVIL DISTRICT COURT
PARISH OF ORLEANS
STATE OF LOUISIANA

GLORIA SCOTT AND *
DEANIA JACKSON *
* NO. 96-8461
VERSUS * DIVISION "I"
* SECTION 14
THE AMERICAN TOBACCO *
COMPANY, INC., ET AL. *
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Transcript of proceedings before The Honorable Richard J. Ganucheau, Judge Pro Tempore, Civil District Court, Parish of Orleans, State of Louisiana, 421 Loyola Avenue, New Orleans, Louisiana 70112, commencing on June 18, 2001.

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Wednesday Morning Session
April 30, 2003
9:41 a.m.
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I N D E X

P R O C E E D I N G S

THE LAW CLERK:
All rise for the jury.
(Whereupon the jury joins the proceedings at this time.)
THE LAW CLERK:
All rise. Oyez, oyez, oyez, Civil District Court for Orleans Parish, Division "I," is now in session. The Honorable Richard Ganucheau presiding. Silence is commanded. Please be seated.
THE COURT:
Good morning.
THE JURY:
Good morning, Your Honor.
THE COUNSEL:
Good morning, Your Honor.
THE COURT:
The objections by plaintiffs' counsel to

the tender of Dr. Rowell as an expert are hereby overruled.

And The Court will recognize Dr. Rowell as an expert in the field of nicotine pharmacology, the effect of nicotine on the body, its relation to smoking behavior and addiction or dependence, and the historical knowledge of nicotine and its actions.

Are you ready to proceed with your direct examination, Mr. Schneider?

MR. SCHNEIDER:

Yes, Your Honor.

Good morning, ladies and gentlemen.

THE JURY:

Good morning.

MR. SCHNEIDER:

Good morning, Dr. Rowell.

THE WITNESS:

Good morning.

MR. SCHNEIDER:

Good morning, Your Honor, learned counsel.

Again, I'm Richard Schneider for Brown & Williamson and we're talking with Dr. Peter Rowell.

DIRECT EXAMINATION

BY MR. SCHNEIDER:

Q. Now, Dr. Rowell, we're now going to get to the subject of your opinions in this case and the various issues of science that you're going to discuss with us today.

Did you oversee the preparation of a demonstrative that can briefly lay out the three areas, three major areas, for your opinions?

A. Yes, I did.

MR. SCHNEIDER:

Bert, can we call up on the screen for His Honor, for the witness and opposing counsel, DDA-2035?

EXAMINATION BY MR. SCHNEIDER:

Q. Dr. Rowell, do you have before you a slide that lists your opinion areas?

A. Yes.

MR. SCHNEIDER:

Your Honor, we would request permission

to publish.

MR. BRUNO:

Judge, we have no objection.

And to make it easy on The Court, we have no objection to any of the slides or any of the documents that they want to use with Dr. Rowell.

THE COURT:

You may publish.

MR. SCHNEIDER:

Thank you, Mr. Bruno.

Let's publish DDA-2035.

EXAMINATION BY MR. SCHNEIDER:
Q. Dr. Rowell, this slide sets out three areas for your opinions; correct?
A. Right.
Q. The first one is "How Nicotine Acts on the Central Nervous System." Are you going to discuss with us that issue today, how nicotine acts on the central nervous system?
A. Yes, I will.
Q. Okay. Dr. Rowell, based on your education, your training and your experience, do you have an opinion as to whether the pharmacologic action of nicotine on the nervous system prevents smokers from quitting?
A. Yes, I do.
Q. And what is that opinion?
A. My opinion is that the pharmacological effects of nicotine are not so severe or strong that they prevent the behavior of cigarette smoking from being -- from quitting.

Q. All right. Now, the secondary opinion is the "Comparison of Nicotine To Other Drugs." And will you compare the effect of nicotine in the nervous system, for example, to the effect of cocaine in the nervous system?
A. Yes.
Q. Okay. Dr. Rowell, based on your education, your training, your experience, do you have an opinion as to whether nicotine is as addictive or dependence-producing as cocaine, heroin and alcohol?
A. Yes, I do.
Q. And what is your opinion?
A. My opinion is based on all the scientific studies and evidence that I've seen, nicotine is very much on the low end of the spectrum compared to the other typical drugs like heroin, cocaine, amphetamine.
Q. All right. And the last area for you main topic of opinion is the "Role Of Nicotine Versus Other Attributes Of Smoking Behavior"; correct?
A. Right.
Q. And let's just bring that back into focus. We talked about it a little bit yesterday. But nicotine is a component of tobacco; correct?
A. Yes.
Q. And you're trying to separate out in those opinions the effect of nicotine as opposed to all the other things associated with smoking?
A. That's right.
Q. And that's what you call smoking behavior?
A. Yes.
Q. All right. And do you have an opinion on

whether attributes of smoking other than nicotine have an effect on smoking behavior?
A. Yes, I do.
Q. And what is that opinion?
A. My opinion is that the very complexity and

repetitive, ritualistic motions of cigarette smoking are very much a determinant of cigarette smoking behavior.
Q. All right. And you're prepared to discuss all of these areas in depth here today with us?
A. Yes.
Q. All right. Now, Dr. Rowell, where does nicotine principally act in the body?
A. Nicotine acts on nerve cells and on specific types of nerve cells which have what are now called nicotinic receptors.
Q. All right. We're going to talk -- go in depth -- You can take that slide down.
We're going to go in depth and talk about how it works in the nervous system, but let me ask you this. When nicotine acts on the nerves in however way it does -- and we'll talk about that -- does it then have effects that can be seen or experienced by the smoker?
A. Yes.
Q. Let's talk about those. What kinds of effects does nicotine have on the body?
A. Nicotine has the same effects that a natural neurotransmitter, acetylcholine, has. And so it produces an increase in adrenaline from the body, which causes a little bit of an increase in heart rate and blood pressure.

Q. Let me stop you for a moment, if I could. Adrenaline, what is adrenaline?
A. Adrenaline is our stress hormone that comes out of a gland, the adrenal medulla. It's kind of the adrenal surge that you get when you're excited or stressed. It causes increase in blood pressure, increase in blood sugar, increase in heart rate.
Q. So if something frightens us, do we get a surge of adrenaline?
A. Yes.
Q. That's what we're feeling when we're feeling aroused?
A. That's right.
Q. All right. What other effects does nicotine have on the body?
A. Nicotine can also work on -- in the peripheral nervous system on other organs a little bit producing changes in pupillary dilation and glandular secretions and things like that through its effect, again, on these receptors.
Q. All right. Does nicotine have any effect on someone's metabolism?
A. Yes.
Q. What does it do?
A. It speeds up the metabolism a little bit through some hormone effects.
Q. Can nicotine have any effect on how much weight you may gain?
A. Yes.
Q. What effect does it have?
A. Well, as a result of increasing metabolism, nicotine actually produces more energy expenditure

during the day. And it can act as a -- it actually produces less weight gain.

Q. All right. Does nicotine have any effect on learning, memory and ability to focus?

A. Yes.

This, again, is a place where the natural neurotransmitter, acetylcholine, is very much involved. And nicotine can improve learning, can improve memory. A lot of tests have shown that. And, actually, there are trials underway for using nicotine and nicotine analogs for Alzheimer's disease, let's say, or memory deficits in humans.

Q. All right. And you say these various effects come out because nicotine is working on the nerves?

A. Right.

Q. All right. Now, you mentioned the peripheral nervous system. Yesterday, you talked about the central nervous system. The peripheral nervous system, those are the nerves outside the brain and the spinal column?

A. Correct.

Q. For how long has it been known that nicotine has an effect on the peripheral nervous system?

A. Since about the 1880s.

Q. All right. And was there research published on that in the published literature from that time period forward about that issue?

A. Yes.

Q. Does nicotine also act on the nerve cells in the brain?

A. Yes, it does.

Q. And for how long has that been known?

A. That was hypothesized, of course, very early on. But the actual experiments to show that came out in about the late 1950s and 1960s. So about 50 years, 40, 50 years.

Q. All right. I want to go now and go into the nerves and talk about how nicotine affects that process and explore that a little bit.

Now, have you prepared a set of demonstratives to explain the nervous system and how nicotine interacts with it?

A. Yes. I hope they'll explain it.

MR. SCHNEIDER:

All right. Let's put up -- Let's publish, if we can, Your Honor, DDA-2039.

THE COURT:

Mr. Bruno has indicated no objections to any of those, so you may publish.

MR. SCHNEIDER:

Thank you, Your Honor.

EXAMINATION BY MR. SCHNEIDER:

Q. All right. Now, let's take a look at this slide together. What are we seeing here, Dr. Rowell?

A. This is the connection between two nerves: The nerve on the left, which I would call the upstream nerve, the nerve where the signal is coming

down; and then the space is called the synapse, which is labeled right here (indicating), this space between two nerves; and then the downstream nerve is the nerve where the signal goes to.

And this is the -- this is the main -- the main area between any two nerve cells or nerves

communicate with each other. This is kind of the business end of the nerve.

Q. All right. So what we're seeing, the two sort of white spaces, those are both nerves?

A. Right.

Q. And the one that's sort of like half of a dog bone there, if you will, that's the upstream nerve?

A. Right.

Q. And those little red dots inside of that nerve, what are those?

A. Yes, these are the neurotransmitters. And these are small chemicals that different nerves contain that transmits the signal. That's why they're called transmitters, so they transmit it to the next nerve.

Q. All right. On the upstream nerve, the ones to the right on the screen, what are the little green things that are labeled "Receptors"?

A. Okay. I would call that the downstream nerve.

Q. I'm sorry.

A. But these are the proteins that are in the membrane of the other nerve. This is a bigger cell body, as you can see. And these are the little locks where the neurotransmitter keys fit into to produce an effect.

So if the neurotransmitter came up and just bumped into a wall, it wouldn't do anything. But they have these little receptors here that can actually fit into -- well, the neurotransmitter fits into the receptor. And that produces the response in the downstream nerve.

Q. So, in other words, one of those little cherry red neurotransmitters comes out of the nerve ending, that's the dog bone end, the upstream one, crosses the synapse, and attaches to a receptor?

A. Right.

Q. And that sends a signal?

A. That sends the signal.

Q. And that's how we're all working every day? That's how our bodies are working?

A. That's the whole system for all our nerve connections in all our body and our thoughts and memories and muscle activities.

Q. So when I wave my arm like this (indicating), somewhere in my body, some nerve is shooting a neurotransmitter and telling my body what to do to make that motion?

A. Right.

As a matter of fact, when you wave your arm, these are nicotinic receptors, acetylcholine

nicotinic receptors, that are being triggered to cause a muscle contraction.
Q. Now, I'm not a smoker, Doctor, currently. You say that I have nicotinic receptors in me?
A. Yes.
Q. Well, why are they called nicotinic receptors?
A. They're called nicotinic receptors because they were, around the turn of the 1800s, the century, to 1900s, they were discovered on the basis of using the drug nicotine to cause muscle contractions. That was an easy thing to measure back then. You could just measure muscle

contractions by putting nicotine on it.
And the theory was that nicotine must be working on something to produce the muscle contraction, and that was called a receptor. And that name has stuck, and now they're called nicotinic receptors.
Q. All right. Nicotine is a component of the tobacco leaf?
A. Yes.
Q. You're saying you take some portion of nicotine -- How do you get nicotine out of a tobacco leaf?
A. You basically just grind up the tobacco leaf and you put in an alkaline solution or a basic solution like ammonia or something like that. And that converts the nicotine to what's called the freebase form, the liquid form. And then you can extract that with an organic solvent like benzene or alcohol or something like that.
Q. All right. And you were saying that back in the early science, when receptors were discovered, they were discovered using nicotine?
A. Right.
Nicotine was actually extracted in pure form in the 1840s, a hundred and sixty years ago. And then they began finding out that it could actually produce muscle contractions through these receptors.
Now, of course, calling these nicotinic receptors doesn't mean that it's nicotine. It stimulates those in the body, because normally people don't have nicotine in their body. But that's the name of the receptors based on the old

finding that nicotine stimulated those receptors.
Q. All right. But, in any event, those things that are called receptors on the downstream nerve --
A. Right.
Q. -- receive these neurotransmitters and send a signal?
A. Correct.
Q. All right. Now, let's talk about neurotransmitters a moment. Are there a number of different types of neurotransmitters?
A. Yes.
Q. And have you brought with you a slide to

explain some of the kinds of neurotransmitters?
A. Yes, there's a number of neurotransmitters. And I put that on a demonstrative slide.

MR. SCHNEIDER:

Let's bring up, if we could, DDA-2040.

EXAMINATION BY MR. SCHNEIDER:

Q. All right. Dr. Rowell, tell us about this slide.

A. Well, this -- these are probably seven of the major neurotransmitters that are in the brain. Nerves, the upstream nerves, those little red balls, could contain any of these chemicals or maybe some others. And that determines what the response will be on the downstream nerve because different neurotransmitters do different things.

And so here are seven major neurotransmitters that are found in the brain and their -- this is maybe a little bit simplified -- but their very general function about what an individual neurotransmitter does.

Q. Let's talk about several of them.

First, I think you've mentioned several times in your testimony so far this first neurotransmitter, acetylcholine.

A. Right.

Q. And that is a neurotransmitter, I'm inferring from looking at the second part of the chart, that affects learning and memory?

A. Correct.

Q. In other words, that neurotransmitter fires when your brain is trying to learn or to memorize?

A. Yes. That's an important neurotransmitter. In fact, that -- those are the nerves, the acetylcholine nerves, that degenerate in patients that have Alzheimer's disease. They lose their acetylcholine neurotransmitters, so they have problems with memory and learning.

Q. All right. We're going to get into this a bit more, but is that the neurotransmitter that nicotine mimics?

A. Yes.

That's an important one, and I have it on top, because that's where nicotine acts to mimic the action of acetylcholine in the body.

Q. All right. And we're going to come back and get into that in a little bit more detail. Let's just talk about a few others on this chart.

Serotonin, some of us might have heard of serotonin. What is the function of that neurotransmitter?

A. That neurotransmitter is involved in mood regulation and also sleep, as I have here. And so,

for example, individuals that are depressed, they take drugs like Prozac and Zoloft which increase serotonin levels. They're called selective serotonin reuptake inhibitors.

Also, the other thing I have here is the

sleep part. And when you eat high protein meals or drink milk and things that have a lot of protein, that contains tryptophan and that makes you sleepy. And so when you drink warm milk or have food or something, you tend to get a little bit sleepy after big meals as a result of the serotonin neurotransmitter.

Q. We'll talk about that in a little bit more detail, but let me ask you a basic question about it.

If a person, a person's body wants that person to go to sleep, I take it the brain will send some signal down a nerve, release serotonin, and that will cause the person to sleep?

A. That's right.

Q. All right. Let's see. We also have on this chart dopamine. Now, what is dopamine?

A. Dopamine is another neurotransmitter. And it is very much involved in the reward or pleasure systems in the body. And that's a focus of a lot of drug-abuse work. And that's why we'll focus on it somewhat.

Interestingly, it also -- I don't have it here -- is involved in motor activity, controlling movement in the body. And patients that have Parkinson's disease have a deficit in dopamine in their body.

Q. All right. And does your body normally release dopamine even if you're not taking any drugs or substances?

A. Sure.

Q. Why is that?

A. The body maintains its kind of normal level of dopamine. And as you go through the day, if you have enjoyable experiences or eat a good meal or things like that, dopamine will modulate. It will go up a little bit. If you have a bad experience or something, feel bad, dopamine can go down. So it's always at a certain level coming out into the nerves.

Q. And are high levels of dopamine associated with feelings of euphoria?

A. Yes.

Q. And are we going to talk about drugs here today that release large amounts of dopamine and cause you to feel euphoric or intoxicated?

A. Right. Drugs that either release or cause the buildup of large amounts of dopamine in that synaptic space.

MR. SCHNEIDER:
All right. Well, let's go back to DDA-2039.

EXAMINATION BY MR. SCHNEIDER:

Q. Now, Doctor, that chart we were just talking about, the neurotransmitters and the different kinds, those are the red dots in this upstream nerve; correct?

A. Correct.

Q. And I think we identified the receptors, but

we didn't identify one of the red blocks that appear on the upstream nerve. What are those?
A. Okay. Those are in almost all nerves and are just reuptake pumps. And that's the way the nervous system itself gets the neurotransmitter after it's been released back into the upstream nerve, the terminal here of this nerve, so that it can be recycled and used again.

So responses that take place don't last forever. And these come back up very quickly, within less than a second, sucks these neurotransmitters back into the presynaptic side, and the response goes away. So it's a continual nerve excitation, release and then reuptake. So those are very important reuptake pumps.

Q. All right. So if a signal is sent down the axon of this nerve right down there --
A. Right.
Q. -- it triggers a neurotransmitter to come out into the synapse; correct?
A. Correct.
Q. It then interacts with those receptors?
A. Right.
Q. Which it's supposed to do for a specified period of time, whatever that is that the body naturally sets up; correct?
A. Yes.
Q. And then it's supposed to, in effect, go home, back to the upstream nerve?
A. Right.
Q. And the uptake pumps, these red uptake pumps, take them back in?

A. They take them back in.
Q. What if they stay out there for a long time?
A. Then you'll get more effect. And as more signals come down, the nerve wire down here, then you actually can build up levels in the synapse.
Q. So if my nerves send a neurotransmitter, I'm stimulated in some fashion, the nerve uptake pump takes them back in, the stimulus ends? But if it remains out there, the stimulus can continue?
A. Yes.
Q. All right. And these basic processes of neurotransmitters, receptors, uptake pumps, crossing the synapse, does this all relate to a variety of drugs?
A. Right.

Well, this goes on all the time in all our cells. That's how we're moving and thinking. And drugs can then come in and interact with some process in this neurotransmitter release system.

Q. All right. And now, Doctor, I think this is obvious. But I take it that nicotine has some relationship to this system we've been talking about?
A. Yes.
Q. And have you brought with you a slide to begin discussing that with the jury?

A. Yes.
MR. SCHNEIDER:
All right. Let's bring up demonstrative DDA-2041.
EXAMINATION BY MR. SCHNEIDER:
Q. Now, explain what we have here, Doctor.

A. Okay. If we're talking about nicotine, nicotine always works by mimicking the natural neurotransmitter, acetylcholine. That's the only place it really works in the body, so --
Q. Can I stop you for a moment?
When you say "mimic," does nicotine have a chemical structure somewhat like acetylcholine?
A. Yes.
Q. And when it comes into the body, the body thinks that it is acting like acetylcholine? That's what you mean by "mimic"?
A. Right.
These nicotine molecules, which I have here in green, come in. And they can fit into the acetylcholine receptor, which is sometimes called the nicotinic receptor, in the same way that the normal acetylcholine molecule. So this is where nicotine works, then this would be an acetylcholine-containing neuron.
Q. Okay. And so since nicotine can mimic acetylcholine, whatever acetylcholine is doing in the body, nicotine can do?
A. Right.
Q. I think we saw a moment ago that acetylcholine helps to improve learning and memory; correct?
A. Yes.
Q. And, therefore, would you expect and is it the case, Doctor, that nicotine mimics that effect?
A. Yes.
Q. All right. Now, we see those green balls there in the synapse.

A. Right.
Q. That represents nicotine?
A. That's nicotine coming in, right.
Q. So I take a puff of a cigarette, smoke goes into my lungs, nicotine is disbursed to the brain, to other parts of the body, and eventually reaches nerves?
A. Right.
Q. These are -- We're talking about nerves in the brain here; are we not?
A. Well, not necessarily. This could be anyplace where there are nicotinic/acetylcholine receptors.
Q. Okay. And one of those places is the brain?
A. The brain is an important site, right.
Q. All right. And it comes into the bloodstream, eventually reaches the nerves, and acts in this fashion that you're about to describe.
Now, tell us what does nicotine do when it

gets in the synapse.
A. Nicotine, let's say, comes in from the outside and then interacts with those acetylcholine/nicotinic type receptors and produces the same kind of signal that acetylcholine would have had it been released. So the receptors don't tell the difference. The main difference is the fact that nicotine lasts longer in the synapse because it's not removed.
Q. All right. Now, we heard a moment ago that when neurotransmitters come out across the synapse, they're taken home by these uptake pumps?
A. Right.

Q. Does that happen with the nicotine?
A. No, nicotine doesn't get taken up by the uptake pumps.
Q. Does it eventually dissipate from the synapse?
A. Yes. It's metabolized fairly quickly.
Q. All right. Now, Doctor, can other substances other than drugs like, for example, food products, can food products act on our nerves in this way?
A. Yes.
Q. Can you give me some examples of that?
A. Well, there are other plant products and animal products that also work with the nicotinic receptors. Then there are plenty of food products that act on other receptors. Caffeine is one, theobromine is another one.
Q. And you mentioned milk and tryptophan a moment ago?
A. Right.
Q. Did you bring a slide with you to discuss this issue of tryptophan working in the synapse of the nerves?
A. Yes.

MR. SCHNEIDER:
Let's take a look at DDA-2046. If we could publish that.

EXAMINATION BY MR. SCHNEIDER:
Q. Now, Doctor, this is a slide entitled "Tryptophan Acts Through Serotonin Receptors"; correct?
A. Right.
Q. You told us a moment ago that serotonin works

-- affects sleep?
A. Yes.
Q. Tell us what we're seeing here in this slide.
A. Okay. This shows another way a drug can work. So serotonin -- I mean, sorry, tryptophan can come in and actually produce an increase in the amount of serotonin neurotransmitter in the synapse.
Q. Now, I'm sorry, tryptophan is what?
A. Tryptophan is an aminoacid that is converted to serotonin, the neurotransmitter, naturally in the body.
Q. And you said, I think you said it's in milk?

A. Yes.
Q. So I take a glass of milk, drink it, it goes into my stomach and eventually reaches my nervous system?
A. Right.
Q. And that represents these little red balls in the synapse here from milk?
A. Right.
This would be increased serotonin from -- you having a big meal, a big turkey dinner with a lot of tryptophan in it for a meal.
Q. All right. A lot of us have heard our mothers and others say, "Get a warm glass of milk and it will help you go to sleep." Is this sort of the effect this is describing?
A. It works a little bit like that. You're not going to go right to sleep, but it increases that probability a little bit.
Q. Okay. Now, I heard you mention theobromine. What is theobromine contained in?

A. That's one of the major alkaloids in chocolate, cocoa.
Q. All right. And have you brought a slide to talk about how theobromine in chocolate gets into the nervous system?
A. Yes.
MR. SCHNEIDER:
Let's take a look at DDA-2047.
EXAMINATION BY MR. SCHNEIDER:
Q. All right. Now, Doctor, what do we have here?
A. Okay. This is yet another way that a drug that's contained in food products can actually work to influence neurotransmitters here. This is now, if we're talking about theobromine, an adenosine-containing neuron. So these red balls are now adenosine.
Theobromine comes in from the outside and can interact with adenosine receptors, which are modulatory receptors all over the brain, to actually block the effect of those receptors.
Q. And, now, adenosine is a neurotransmitter?
A. Yes.
Q. And is it a neurotransmitter that has an effect on the degree in which you feel stimulated and awake?
A. Well, actually, adenosine is an inhibitory effect. So adenosine tends to depress nerve activity on nerves where those receptors are, and theobromine blocks that effect, and that's where you get the excitation.
Q. All right.

A. So it does cause a stimulation through preventing the adenosine from causing its effect.
Q. So when you eat some chocolate, you can feel a little, maybe a little pepped up?
A. Stimulated, right.

Q. How about caffeine? Does caffeine work on these adenosine receptors as well?
A. Right.
Caffeine actually even better on the adenosine receptor, but it works through the same system. So caffeine comes in, blocks the inhibitory adenosine receptors and produces excitation.
Q. And all these things we've been talking about, tryptophan, theobromine, caffeine, when it has this effect, is that a drug effect?
A. Yes.
Q. Even though we're drinking coffee, having chocolate and drinking milk, we don't think of it as taking drugs but it's a drug-like effect?
A. Well, it's a drug-like effect.
If it's in food and natural products, they will cause those effects. If you take a substance for the purpose of producing the effect, then it more or less becomes a drug.
Q. All right. Now, I mean, is it necessary to have a substance in the body, whether it's a drug or a food, to have an effect on nerves?
A. No.
Q. Can behaviors have an effect on the release of neurotransmitters?
A. Sure.
Q. Can you give us an example?

A. Well, all of our behaviors are having an effect on our mood and our -- effects all the time. For example, when we were talking about the dopamine system, just pleasurable activities or activities that have to do with increasing our survival value, our brain says we like you to do that, like eat, eat a high-fat or high-sugar meal, that feels good, do it some more. Because the body thinks that's good for you. So, there again, dopamine, which is our feel-good hormone, can be affected by behaviors.
Q. Well, I mean, for example, if I like to go to a casino and gamble, can that have an effect on dopamine in the body?
A. Yes.
Q. So just the behavior that I'm doing can have an effect on my nerves releasing dopamine, for example?
A. Yes.
Q. Now, we talked about the relationship of nicotine to acetylcholine. Does nicotine only result in the release of acetylcholine or does it also affect other neurotransmitters?
A. Nicotine always works through those acetylcholine receptors. But those receptors, the nicotinic receptor system or the acetylcholine receptor system is a system that modulates a lot of neurotransmitters.
As a matter of fact, all of the neurotransmitters, those seven I had up on the previous slide, can be modulated by acetylcholine nerves that exist naturally in the body.
Q. All right. So separate and apart from any

drug, let's just talk about acetylcholine for a moment. Acetylcholine nerves can lead to the release of dopamine in other nerves through its action?
A. Right.
Q. And nicotine can also have that effect?
A. Yes.
Q. Can caffeine have that effect?
A. Yes.
Q. Now, we talked a bit already about dopamine and that we call it the pleasure neurotransmitter; would that be fair?
A. Yes.
Q. All right. And is that something that scientists, pharmacologists like you, study to determine the dependence potential of various substances?
A. Right. By looking at the amount of dopamine that can be released.
Q. All right. And nicotine, through its actions, can ultimately increase the release of dopamine; correct?
A. Yes.
Q. Now, have you brought a slide to begin to show this process?
A. Yes.

MR. SCHNEIDER:
Let's put up DDA-2042.

EXAMINATION BY MR. SCHNEIDER:
Q. All right. Now, Doctor, here this looks a lot like this slide we've been seeing, of course. Tell us what we're seeing here.

A. Well, it's a little more complex. Because now what happens is nerves in the body, a lot of nerves in the body, contain receptors on the upstream side which are now here (indicating) -- these are presynaptic receptors they're called -- which modulate either stimulatory by nicotine or nicotinic receptors or inhibitory by adenosine receptors those other neurotransmitters.

So here we have a dopamine neuron, the feel-good neurotransmitter. And the release of dopamine into the synapse can be modulated by the acetylcholine receptors that are here that nicotine mimics. The body normally does that through its own acetylcholine release; but, once again, nicotine can fit into those same receptors and produce the same effect that the natural neurotransmitter, acetylcholine, produces.
Q. All right. So nicotine comes into the body, works on the receptors on this dopamine nerve, and ends up causing a release of dopamine?
A. Right.
Q. Which will lead to some pleasurable feeling?
A. Right.
Q. Now, how about caffeine? Does it do something similar?
A. Yes.

Caffeine would work on the other modulatory system that a lot of neurotransmitters have, which are the adenosine receptors we talked about.

MR. SCHNEIDER:

Let's pull up DDA-2043.

EXAMINATION BY MR. SCHNEIDER:

Q. What are we showing here?

A. This would now be an adenosine effect on these inhibitory neurotransmitters. So, again, it's still a dopamine neuron. And adenosine can come in and -- caffeine, rather, caffeine would be a drug that could come in and block that inhibitory adenosine effect that the body normally uses adenosine for.

This gets a little complex. It's really kind of the same lecture I give to medical students, so we're learning the medical student system here through the adenosine inhibitory receptors and the nicotinic/acetylcholine receptors' excitatory effect.

Q. And, Doctor, ultimately all of the discussion that you're doing here today, is that going to help us compare nicotine, caffeine, cocaine and heroin in terms of how much effect they have?

A. Yes.

Because the point here is that caffeine and nicotine work through a natural system of the body, that the body already has in place for releasing adenosine or releasing acetylcholine to work on those specific receptors as opposed to the other psychostimulant drugs like cocaine and amphetamine, which we'll talk about how they work in a minute.

MR. SCHNEIDER:

All right. Let's take a look at a slide for cocaine. Let's look at DDA-2044.

EXAMINATION BY MR. SCHNEIDER:

Q. Now, Doctor, this is a slide that says "Cocaine Increases Dopamine Levels by Blocking Its

Removal from Synapse"; correct?

A. Right.

Q. Now, before when we were talking about nicotine and caffeine. They actually stimulate nerves and lead to the release of dopamine; correct?

A. Yes.

Q. What we're saying here is that cocaine blocks removal. Explain this to us.

A. Okay. Cocaine comes in and blocks the ability of those uptake pumps to remove dopamine from the synapse. So dopamine levels build up to very high concentrations.

And one of the important points here is that this is not a natural system, a physiological system that the body has. There is no substance in the body that blocks those pumps naturally. So it's kind of an artificial effect to prevent that dopamine uptake.

Q. All right. Doctor, this is a fair amount of

science to absorb.
A. Right.
Q. So sometimes I'm going to repeat things to make sure that I'm understanding it.
Those uptake pumps, those are the things that you mentioned earlier, take neurotransmitters out of the synapse and bring it home back to the nerve?
A. Exactly.
Q. And what you're saying is that cocaine blocks those uptake pumps so it can't take the chemical out of the synapse?
A. Yes.
These will come in and cover up those uptake

pumps so they can't bring the dopamine back in, so the dopamine stays out in the synapse.
Q. And what is the import of that? So what if the dopamine stays out in the synapse?
A. Well, you get more dopamine stimulating these dopamine receptors that are on the downstream side of the nerve so you get more of a pleasure effect. And then other transmissions will come down because that happens all the time. And more and more dopamine will continue to come out and build up in the synapse.
Q. All right. So as dopamine is, if you're taking cocaine, dopamine is being released out into the synapse, cocaine is blocking it from taking it back in, and more and more and more of it is building up in that synapse, and that's what's causing people who take cocaine to feel euphoric?
A. Right, because these are our -- that's our feel-good neurotransmitter. If you build up very high levels because you can't ever get it back in the system, you get a real euphoric effect.
Q. All right. Now, does the same thing happen with amphetamines?
A. A similar thing happens with amphetamine, yes.
MR. SCHNEIDER:
Let's briefly look at that, DDA-2045.
EXAMINATION BY MR. SCHNEIDER:
Q. This is amphetamine. What is amphetamine?
A. Amphetamine is sometimes called speed. It's a compound that, again, fools these uptake pumps to interact with the uptake pumps. It looks like a

very similar structure to dopamine, actually.
Q. Now, you said that caffeine and nicotine sort of mimic natural chemicals in the body and work on natural processes; correct?
A. Right.
Q. But cocaine and amphetamine block uptake pumps. Is that a natural process?
A. No.
Q. That's doing something different than what the body normally does?
A. Yes. There's no system in the body that we have that blocks those uptake pumps.

Q. All right. Well, we've seen that nicotine, caffeine, cocaine, amphetamine can all lead to a release or at least a buildup of dopamine in the synapse.

Is there any way to compare these drugs?

A. Yes.

Q. Is there a way to compare them to determine how much dopamine is released by nicotine, caffeine, cocaine and other drugs?

A. Yes. You can actually do experimental studies to measure the amount of dopamine that's released in response to those drugs.

Q. Does it matter how much is released in terms of comparing them? Why do we care how much?

A. Well, because the more dopamine that you get in the synapse, the greater pleasure or positive reinforcement effect you would expect that drug to produce.

Q. Well, would it be fair to say, Dr. Rowell, that if a drug ends up increasing the dopamine in

the synapse a great deal, it is a drug that has much more of a dependence potential than a drug that increases dopamine release slightly?

A. Right.

Of the number of factors that you could measure, that would be an important determinant of what you would expect the drug to produce as far as its potential for dependence, right.

Q. All right. So what we're actually talking about here is we're going to figure out some way to measure the amount of dopamine in the synapse?

A. That's correct.

Q. Now, have scientists done studies that actually enable them to test the amount of dopamine released by these various chemicals?

A. Yes.

Q. Have you yourself done that kind of research?

A. Yes.

Q. Does it involve animals?

A. Yes.

Q. And does it involve in some way measuring physically how much dopamine is released in the synapse of nerves?

A. Right.

Do you want me to explain a little bit about that?

Q. Yes, you can. Let me ask you just a couple of other questions.

A. Okay.

Q. This whole field of studying these levels in animals, is that common in the field of pharmacology?

A. It's very common. In fact, it happens every time that you study drugs, right.

Q. And are animal studies and animal tests the way in which pharmacologists evaluate drugs and predict their effects on humans?

A. Right.
The animals, mammals in particular, mammals have in these lower brain centers, the pleasure centers of the brain, which are kind of primitive centers, the exact same anatomy as human beings. Humans have a much bigger cerebral cortex, thinking, intellectual place.
But as far as these lower brain centers, the anatomy and the areas of the brain, the nerve connections are just the same. And so there are experiments that we can do in animals that we just cannot do in human beings.
Q. What is that lower brain center called?
A. That's the mesolimbic system in this area would be called the nucleus accumbens.
Q. All right. And so the nucleus accumbens is sort of the primitive center of the brain?
A. Right. It's a little bit forward in the brain, kind of at the very base of the brain.
Q. And do animals have neurotransmitters as we've been describing?
A. They have the same neurotransmitters.
Q. And the same sort of nervous system setup --
A. Yes.
Q. -- as human beings?
A. Yes.
Q. Now, Doctor, you wanted to explain a moment

ago and I asked you a few more questions -- for which I apologize -- but tell us how it is that you can measure the amount of dopamine in the synapse of animals.
A. Okay. That's why these are done in animal studies, because you have to put a probe down in the brain to actually measure the amount of dopamine that comes out. So human beings, obviously, complain if you'd try to sink a probe down into their brain.
So we take an animal and put them in an apparatus that can very precisely center the bottom of that probe in this nucleus accumbens area. And then the fluid is taken up, and it's put through what's called a gas chromatograph, and you can measure the dopamine that was released when you injected the animal with certain drugs.
Q. All right. What is that process referred to?
A. It's called microdialysis.
Q. All right. And when you refer to a probe, as we're looking up at this diagram here, DDA-2045, would it, in effect, be as if I took my pen and inserted it into that synapse space so that you can draw up, up through the bottom of my pen, draw up the dopamine that's then being released in that synapse?
A. Right, more or less.
This is one neuron. And the nucleus accumbens, obviously, has thousands of these identical neurons in there. The probe is actually about the size of a human hair, so it's very small. But on this picture, it would be fairly large. And

would come in and pick up that dopamine, right.

MR. SCHNEIDER:

Let me ask you, if we could, take a look at a document admitted yesterday, GK-000554. If we could put it up on the screen for counsel and His Honor first.

Your Honor, this was a document admitted yesterday. We would request permission to publish it, particularly the second page.

MR. BRUNO:

As I said, Judge, I have no objection to any of this.

THE COURT:

You may publish.

MR. SCHNEIDER:

Let's go to the second page. And how about highlighting that title?

EXAMINATION BY MR. SCHNEIDER:

Q. Now, Doctor, this is the article we talked about yesterday that you authored; correct?

A. Yes.

Q. That I was mispronouncing various words in there. But this is your work studying the release of acetylcholine in the brain system; correct?

A. Right.

Q. And to do these kinds of studies, did you also use microdialysis techniques or other techniques?

A. In this study -- and we've done those on other studies with dopamine -- we used a technique called in vitro superfusion, which measures the ability of the nerve to release the neurotransmitter

in a little different way. And that's by making it radioactive. So that little 3H part right here (indicating) means that that's a radioactive tracer for that neurotransmitter.

Q. All right. Let's take that down and let's bring up another slide. But let me ask you a preliminary foundation question.

Have you reviewed the scientific literature in the field of pharmacology that reports on the dopamine levels found in various animal systems using various drugs?

A. Yes.

Q. And have you prepared a chart to assist the jury and us in the courtroom in understanding the relative degrees of dopamine released by various drugs?

A. Yes.

MR. SCHNEIDER:

Let's pull up DDA-2048.

EXAMINATION BY MR. SCHNEIDER:

Q. Now, Doctor, can you take us through this chart and tell us all what it means and explain the graph to us, if you would.

A. Okay. These are -- This is the microdialysis experiment where you measure the dopamine levels in the synapse that comes out with these various drugs.

This is a measure of the percent increase that occurs with the dopamine that goes up over a one-hour period after the drug is injected.

And so it simply compares in -- These studies were done in rats, experimental laboratory rats. The probes were inserted down in the nucleus

accumbens area. And when these drugs were administered, this is the percent increase that was produced by various drugs.

Q. All right. So down at the bottom, you listed the various drugs that were tested and reported in the literature; correct?

A. Correct.

Q. And amphetamine there, if I'm reading this chart correctly, when it was administered, it increased the amount of dopamine in the synapse over normal levels by 550 percent?

A. That's right.

Q. Is that what that chart is showing?

A. Yes.

Q. And cocaine increased the level of dopamine in the synapse by 350 percent?

A. About, right.

Q. Right.

And morphine was slightly more than 300 percent?

A. About 320, right.

Q. And then if you go down to nicotine and caffeine, they're in the range of 100 percent or less?

A. Right. 104 percent and then 68 percent, I think it is.

Q. Okay. In terms of the information presented in this chart, what does it tell you about the relative strength of nicotine and caffeine compared to these other drugs?

A. Well, this demonstrates that there's a spectrum of activity with all drugs, as you would

expect. Some drugs are very strong drugs, very active drugs; and some drugs are relatively weak.

And on the ability of drugs to increase the levels of dopamine in the pleasure center of the brain, I think I can see from this that nicotine and caffeine are on the low end of the spectrum for the ability to increase the levels.

Q. Okay. And dopamine is the substance that is studied by pharmacologists to predict how dependence-producing a chemical might be; correct?

A. Yes.

Q. And based on this chart and the data in this literature, what does it lead you to conclude about the relative dependence-producing ability of nicotine and caffeine versus these other drugs?

A. Well, even if you had no other information, with this you would expect that nicotine would have a low potential for producing a drug dependence in relationship to amphetamine, cocaine and morphine.

Q. All right. Now, you mentioned a moment ago -- or maybe even longer than a moment ago -- that behaviors can affect dopamine levels; correct?
A. Correct.
Q. Have you reviewed the scientific literature that studies the release of dopamine under various behavior situations and compares that to nicotine and caffeine?
A. Yes.
Q. And have you prepared a demonstrative that will allow us to make that comparison?
A. Yes, I have.
MR. SCHNEIDER:

Let's put up DDA-2049.
EXAMINATION BY MR. SCHNEIDER:
Q. Now, Doctor, this demonstrative is entitled "Behaviors Affect Dopamine Levels." Can you explain this chart to us?
A. Okay. This was, again, necessarily an animal study because we used the microelectrode -- microdialysis probes to go down into the nucleus accumbens to, again, measure the amount of dopamine release. And this is the same thing. It's the percent increase over 60 minutes. The scale is a little different because these don't go up to 600 percent.
But in these animal studies, we -- the individual cited down here took animals, for example, with a thirst, that were thirsty, they had been deprived of water for awhile; and when they were exposed to the water and allowed to drink, the dopamine levels go up. As I said, the body uses this system to say, "This is something you ought to keep doing."
Q. All right. So in this particular one where it says "Quenching Thirst," you were able to go into the nerve system, the synapse of the animal -- And what kind of animal was it?
A. These are rats.
Q. -- a rat and actually measure the dopamine level increase in the brain when they have that satisfactory quenching thirst after being deprived of water for some time?
A. Right.
And the way the experiments are done is the

microelectrodes are inserted down their -- The actual surgery is done a week ahead before you do the experiments. And the animals get used to it. They wake up, they're freely moving, they're running around the cage but they have a little probe on them. And then you can measure their normal level.
And when you deprive them of water in this case, for example, then when they drink, you get the big increase.
Q. All right. How about the next bar? What it says is quenching thirst has about a 300 percent release of dopamine; correct?

A. Yes.
Q. Which, remembering back to the prior chart, was in the range of how much is released for cocaine or morphine?
A. Right.
Q. Looking at eating, what is that telling us?
A. Well, these are food-deprived animals. They haven't had food for 24 hours, I think it was, so they're hungry. And when they are given access to their food, once again, the dopamine levels go up.
Q. All right. And they go up to about a 250 percent increase?
A. Right.
Q. I don't want to go into the next one too much. But what is that bar telling us?
A. Well, these are male rats. And they are exposed to a female in heat. And when they are allowed to interact with the sexual activity, the dopamine levels go up. This is another thing that the body thinks is a good thing to do.

Q. All right. And on nicotine and caffeine, those are the levels carried over from the prior chart?
A. Right. This was -- These are exactly the same increases that were on the previous charts, the same study exactly.
Q. And from this demonstrative and this study of the literature, what conclusion, if any, do you reach, Doctor?
A. The point of this is really that you don't need drugs to increase dopamine levels, that normal behaviors can do it and pleasurable behaviors can do it. So it doesn't necessarily have to be a drug effect. And, as a matter of fact, some activity that you have can produce actually fairly high levels of dopamine.
Q. All right. Now, we've looked at the release of dopamine and various chemicals, we've compared that to behaviors. Are there studies in the pharmacologic literature that compare how human beings evaluate the differing effects of drugs that they take?
A. Yes.
Q. And how are those studies performed?
A. Okay. Well, when you're dealing with human beings, you obviously can't insert a microdialysis probe down in their brain and do these kind of surgical studies. So the quantification of the drug effect has to be much more subjective.
You basically just ask the individual, compare different drugs and see how they compare to a placebo effect. Which would be basically

saltwater injection, let's say. So you say, "Does this feel good?" And then here's a drug.
The studies, by the way, are done what's called blind in the fact that the humans don't know whether they're giving an injection -- getting an

injection of, let's say, nicotine or cocaine or saline, saltwater, so --
Q. All right.
A. But it's a subjective scale.
MR. SCHNEIDER:
Let's put up DDA-2051.
EXAMINATION BY MR. SCHNEIDER:
Q. Now, Doctor, this graphic is entitled "How 'Good' Do These Drugs Make You Feel?" Correct?
A. Yes.
Q. And it's hard to see, but the source at the bottom of that is an article written by Dr. Henningfield; correct?
A. Right. This was an article by Jack Henningfield.
Q. And Dr. Henningfield is one of the witnesses who have testified in this case. Are you aware of that?
A. Yes.
Q. All right. Tell us about this graphic and what it shows us.
A. Okay. In this study, this is, again, a score of zero to six. Basically, the individuals were asked to rate the pleasurable activity of these different administrations. And this is the increase that these drugs produced above the placebo effect, basically the saltwater injection.

Q. Okay. Let me stop you there. Placebo, what does that mean?
A. Placebo is the control for the fact that a lot of times individuals, because they don't know whether they're getting the drug or not, they'll report that a drug does an effect or that the administration does an effect when it really doesn't.
In any good drug study, you always put a placebo in to try to control for the unconscious thinking that there was some effect coming from just taking a sugar pill, let's say.
Q. All right. So somebody who's involved in a study, they know they're involved in a study of how a drug makes them feel, and so they get an injection, and they may say it makes them feel good, even if it's water, and that's the so-called placebo effect?
A. That's the placebo effect.
Q. And what this chart tries to test out is over that reported placebo effect what euphoria did people feel?
A. Right, was there an increase comparing the placebo to the drug and what percent increase was that.
Q. All right. And tell us about that for each of these substances.
A. Well, again, morphine is rather high, it makes people feel good; amphetamine; pentobarbital, which is one of the barbiturate compounds that people can use; ethanol. In this study, there was no caffeine, there was no cocaine used. But for

these drugs, those are the increases over placebo that were reported.

Q. All right. Now, ethanol is what? What's the common term for that?

A. That's drinking alcohol.

Q. Okay. And in this particular study, persons who took these various substances, nicotine, the report was that it made them feel slightly better than the placebo --

A. Yes.

Q. -- compared to all the other chemicals which made them fell materially more better than the placebo?

A. Right. There was a bigger increase over the placebo effect with those other drugs.

Q. All right. Now, we talked about dopamine levels compared to behaviors, we talked about the extent of euphoria. Is there any other concept in the pharmacologic field that pharmacologists use to evaluate the strength of substances?

And what I'm referring to here is reinforcement.

A. Yeah, reinforcement is kind of the process of trying to evaluate in animal studies how good things feel. Because you can't ask an animal, "Does it make you feel good?" So you put on a term called reinforcement.

Q. Right.

Typically, you can't ask a mouse, unless it's Stuart Little, how it feels. So reinforcement is the way that they do that?

A. Right.

Q. And what is reinforcement?

A. Okay. Reinforcement is typically measured in animal studies on the ability of the animal to respond to get the drug. So if a -- And this would be like a bar-pressing behavior, for example.

So the animal can't tell you it feels good; but the animal can say I'm going to press a bar the whole bunch of times to get that reward, let's say.

Q. All right. So if you have a mouse or a rat in a cage, you evaluate reinforcement by how hard they will work to get the substance?

A. Right. It's just another way to try to compare drug pleasure, drug reinforcement.

Q. For example, if you have a cage and you have two spouts going into the cage which are both water, you would expect the animals to go to each spout equally and work equally hard because there's no differential between the two?

A. Right.

Q. And in terms of testing or counting how reinforcing a substance is, how is that done specifically?

A. Okay. Again, with drugs, what you normally are going to inject, rather than just put them in the water because you get there quickly and some drugs are metabolized, so what you do is you allow

the animal to administer the drug to themselves by pressing a bar. This is called drug self-administration.

And normally, like you said, we'd have two bars. One would be the actual drug-injecting bar and the other one would be more or less the placebo

bar, the saltwater bar. And so you would compare the number of times that the animal would press the bar to get the reward or the drug.

MR. SCHNEIDER:

All right. Well, Your Honor, we're going to go into that chart in a moment.

But given that it's 10:45, if Your Honor would like, we can take our morning break.

THE COURT:

We'll take our mid-morning recess at this point until 11:00 o'clock by the wall clock.

(Whereupon the jury is excused at this time.)

THE COURT:

Let the record reflect the jury has left the courtroom.

Anything for the record by plaintiff counsel?

MR. BRUNO:

No, Judge.

MR. RUSS HERMAN:

Nothing, Your Honor.

THE COURT:

Defense counsel?

MR. WITTMANN:

No, Your Honor.

THE COURT:

We'll recess until 11:00.

MR. RUSS HERMAN:

Off the record, could I approach with Mr. Sholes for just one moment?

(Whereupon a brief recess was taken at this time from 10:45 o'clock a.m. to 11:02 o'clock a.m.)

THE LAW CLERK:

All rise for the jury.

(Whereupon the jury joins the proceedings at this time.)

THE LAW CLERK:

All rise. Recess is over. Court will come to order.

THE COURT:

Please be seated.

Mr. Schneider.

EXAMINATION BY MR. SCHNEIDER:

Q. Good morning, Dr. Rowell. Let's continue. We were talking about reinforcement.

A. Right.

Q. And you were describing laboratory research involving laboratory animals who were in cages;

correct?
A. Yes.
Q. And when you were testing two different substances, like water versus a drug, do I take it that the animals are hooked up in some way to an I.V.?
A. Yes.
Q. And one bar in the cage might be attached to an I.V. that had cocaine in it and another bar might contain water?
A. Right.
Q. So if they went to one bar and tapped on that bar, they'd get an injection of water?

A. A little injection of, right, saltwater, actually.
Q. Saline?
A. Right.
Q. Okay. Or if they hit the other bar, they would get an injection of cocaine?
A. The drug, right.
Q. Or whatever the drug being tested is?
A. Correct.
Q. And these tests of -- The degree to which a chemical is reinforcing is a common test in the field of pharmacology?
A. Yes.
Q. To do what?
A. To measure the reinforcing value. Basically, you're asking the animal in a roundabout way how good did this drug make you feel? Do you want to continue to press the bar to get that drug or not?
In fact, some chemicals that you can put in make the animal not want to press the bar. They are negatively reinforcing or dysphoric.
Q. All right. And in terms of nicotine, how does nicotine compare with drugs like cocaine and morphine in terms of reinforcement?
A. Well, it's weak. It's a weak drug compared to those drugs.
Q. Do laboratory animals automatically hit a nicotine bar if it's placed in the cage?
A. No.
Q. Has nicotine been found to be reinforcing in laboratory animals?
A. Yes.

Q. Have there been tests or procedures developed by pharmacologists and others who study to, in effect, teach laboratory animals how to use nicotine?
A. That's right.
Q. Can you explain that to us, that whole process of training and why you need training?
A. Well, the drug self-administration procedure for animals in testing drugs was developed 40, 45 years ago. And with the very pronounced drugs of dependence, cocaine, for example, if you put a cocaine lever and a saline lever in the cage, the

animal will just curiously walk around and knock into the cocaine lever. And within days, they will be administering themselves cocaine quite effectively.

And that's happened with a lot of drugs. Nicotine, of course, was always thought to be a drug of reinforcement which would produce this, but it was very difficult to get animals to learn to self-administer nicotine. And the process has developed slowly so that now it is possible. And we know that it is reinforcing.

But for rats to begin their self-administration of nicotine, normally you have to food-deprive them a little bit and they are then trained to press the bar in response to food reward. And then nicotine is substituted for the food-reward lever and they learn to associate that with, also, some pleasurable effect.

And there's a specific -- It's a very critical dose. It's about 30 milligrams per

kilogram dose that you have to give them and a ratio of one to five. So they have to press the lever five times to get the one injection.

And these are very critical things that researchers have finally -- I guess what I'm getting at is researchers have finally learned how to train animals to show that nicotine is, in fact, a reinforcer and does produce self-administration behavior.

Because if you, for example, if you switch bars, which you always do in these studies, to make sure they just didn't always go left, then they will then move to the bar that has the drug. And so, clearly, nicotine does it. But it's dramatically different than cocaine and amphetamine.

Q. All right. So when you have an experiment in which you're using cocaine and you're putting the animal in that cage for the first time, and there's cocaine and water, saline, water --

A. Right.

Q. -- the animal may accidentally bump into the cocaine bar and learn on its own to take that cocaine?

A. Yes.

Q. But when you have pure nicotine in the cage versus saline, and the animal bumps into the nicotine bar, gets an injection of pure nicotine, absent training, it's not going to keep coming back to that in a way different from the saline bar?

A. Right.

And the other thing you have to do, which I neglected to tell you, you have to compare the

nicotine bar with environmental cues. Normally, that's lights blinking or lights going off when they get the injection.

The animals -- Rats, in particular, are nocturnal animals. They don't like to be in bright

lights. And if the lights go out when they press it, that tends to be reinforcing. And that usually has to be continued with the injections.
Q. All right. Now, Doctor, have you brought with you a demonstrative to explain this reinforcing comparison that we've been discussing?
A. Yes.
Q. Has there been scientific literature that reports how reinforcing cocaine is or other drugs versus nicotine?
A. Yes.
Q. And you've reviewed that literature and based this demonstrative upon that?
A. Yes, I have.
MR. SCHNEIDER:
All right. Let's pull up DDA-2050.
EXAMINATION BY MR. SCHNEIDER:
Q. Now, Doctor, we are talking about this chart but let me ask you a few questions about reinforcement generally that I didn't pick up so far.
How long has it been known that nicotine can have a reinforcing effect on animals?
A. The first administration studies were done actually in primates in the late '60s, 1960s. But most of the studies were in the 19 -- late '70s and around 1980. So it's been 20, you know, 30, 25

years.
Q. All right. Let's go to this demonstrative now and explain to the jury what this chart shows us.
A. Okay. This is the number of daily injections that the animal, in this case rats again, will respond to on the lever that produces the drug. And so here we have the number of daily injections. And then different drugs that were put in.
In this case, this one laboratory by Collins trained the animals to administer nicotine. And then he also tried caffeine and just basically the placebo effect of saline, which animals will, you know, bump into a couple of times a day. Maybe 15 times they might hit the saline bar. And it just measures the number of responses.
Q. All right. So with respect to cocaine, over the course of a day, the laboratory animal will work to get 300 injections of cocaine?
A. Just about 300, right.
Q. Or just about. Okay. And morphine, 200 plus?
A. Yes.
Q. And amphetamine, which is speed, 150 plus?
A. Yes.
Q. And then we have nicotine, caffeine and saline. And nicotine, is that around 28 administrations a day?
A. That's right. That's what it is.
Q. And caffeine is -- What is that? 23?
A. I think that's the number, correct.
Q. And saline is what? Can you tell from that

chart?
A. No. This was reported right in the paper by the numbers, so this is just the chart.
Q. But somewhat slightly less than caffeine and nicotine?
A. Yes.
Q. And based upon this data, what conclusions do you reach?
A. Well, it's another line of evidence that nicotine is a reinforcer; but it's a weak reinforcer when compared to other drugs that would typically be thought of as drugs of abuse or drugs of dependence.
Q. All right. Now, all of these factors we've looked at so far, the degree of dopamine release, the comparison of dopamine release from nicotine to behavior dopamine release, the reported euphoria or euphoric feelings of each chemical, and this reinforcing data, does all of that factor into how a pharmacologist evaluates the dependence-producing potential of a substance?
A. Yes.
Q. And in terms of a drug like cocaine, for example, does it score higher in all of those areas than nicotine?
A. Yes.
Q. And is it substantially higher?
A. That's my reading of the information, yes.
Q. All right. Have you prepared a chart that summarizes the dependence potential of various different drugs?
A. Yes.
MR. SCHNEIDER:

Let's pull up DDA-2052.
EXAMINATION BY MR. SCHNEIDER:
Q. Now, Doctor, this is a graphic entitled "Dependence Potential of Drugs." Can you walk us through the entries in this demonstrative and tell us what it means?
A. Okay. This actually comes right out of a medical pharmacology textbook called Integrated Pharmacology by Page, 1997. And they have a chart which compared the drug dependence potential of a number of compounds.
And there are two columns here. Drugs can have a dependence potential by virtue of them having a lot of reinforcing value; in other words, you get a big high, it makes you feel really great. For example, cocaine would do that. It's a very strong drug. Or -- Actually, and/or a drug could have a dependence potential because it has a lot of what's called physical dependence or physiological dependence, which means that you continue to take the drug because you have to take it to not suffer withdrawal symptoms.
So there's pronounced physical dependence on the drug. It may not make you feel as great as some other drug like cocaine; but if you don't take it, you have very severe withdrawal symptoms and

tolerance. So we have more or less reward or psychological dependence is what it's called in this textbook and physical dependence.

And, normally, it's thought that for a drug to be -- to have a large dependence potential, it would have to be at least moderate or high in one of these categories and perhaps both.

So basically from this textbook, they categorized morphine and heroin, the two major opioid type responses, methadone, which is another little bit weaker opioid, alcohol, cannabinoids, which is the marijuana, cocaine, amphetamine, PCP, the barbiturates and benzodiazepines, which are like Valium, with their dependence potential for either physiological reward, euphoria, let's say, or feeling good with pronounced physical dependence.

And nicotine and caffeine were also on the table. And they -- and I agree with this -- they produce rather weak euphoria. You don't really get a big high if you inject someone with nicotine. And the physical dependence, the withdrawal is, I would categorize it again, as they do, as mild or weak compared to these other drugs that have strong physical dependence like the heroin compound.

Q. And when we talk about dependence, this is talking about substances that cause or exhibit in their users a craving and a repeated use of that substance?

A. Right.

Q. And you have another column on there called "Controlled Substance?" What does that refer to?

A. This determines whether these drugs are controlled by the Drug Enforcement Administration. There are schedules of drugs that you have to have a license for to use. And this is based on their dependence potential.

The Schedule 1 drugs have a very high dependence potential and no therapeutic value; Schedule 2 has some therapeutic value, but also high; 3, 4, 5.

So, in other words, to -- For example, as I mentioned earlier, I use cocaine and amphetamine in my laboratory. In order for me to use those drugs, I have to apply for and be granted a drug -- a license by the Drug Enforcement Administration; I have to fill out very precise paperwork to order that drug; it can't be shipped by carrier, it has to come in a separate container, special delivery; I have to put it under double lock and key; and, very importantly, I have to inventory that drug.

Anytime I take a milligram out of the cocaine bottle, for example, I have to say how I used it, what experiment I used it in. If I want to destroy the drug, I have to get people come in and observe it and they sign off on the fact that the drug was destroyed because I didn't need it anymore.

I mean, there's just a whole procedure for

going through Drug Enforcement, DEA licensing. And it's, of course, illegal to walk around with these drugs without special permission, I guess.

And, of course, again, here nicotine and caffeine do not require a DEA license. I order those and use them in my lab, and they're not locked up.

Q. All right. So all of the substances that have strong dependence potential are all controlled substances by the Drug Enforcement Agency?

A. Yes.

Q. But caffeine and nicotine are not so controlled by the Drug Enforcement Agency?

A. Correct.

Q. Now, you say that you use nicotine in the work that you do?

A. Right.

Q. And are you able to order nicotine freely without getting a license?

A. Sure.

Q. Have you brought with you an example of the kind of nicotine that you order to do your research?

A. Yes.

Q. Why don't you show it to us?

A. Okay. I've got it in my pocket here. It's just a chemical bottle of nicotine, pure nicotine.

MR. SCHNEIDER:

I'm going to ask that -- I've taken a picture of that bottle. I'm going to ask if we could put up DDA-2037.

EXAMINATION BY MR. SCHNEIDER:

Q. Now, Doctor, explain to us what it is that you have in your hand and what we're seeing up on the screen.

A. Okay. I just took a picture of this in my laboratory. And it's a bottle of nicotine that, in this case, I order from a company called ICN Biomedicals. It's a pure nicotine salt, which is sometimes called the bound form of nicotine. And you can also order the liquid freebase form of nicotine.

Q. So what's in your bottle is not liquid but a salt?

A. Right. It's just the little nicotine crystals here. I mean, --

Q. Nicotine crystals are down at the bottom.

A. Right.

Q. We could pass that around to the jury, if they wanted to, but --

A. Sure.

Q. But the bottle that you're holding is depicted up on the screen?

A. Right. That's this bottle (indicating).

Q. And you don't have to get permission from the federal government to purchase that or get a prescription for that?

A. No. It's not illegal for me to have this or

take it through the airport or anything.
Q. And could I order it?
A. Yes.
Q. Do you have to be a scientist?
A. No, you could order nicotine.
Q. Any member of the public can order it?
A. Sure.
Q. Now, Doctor, have you received any reports that there are people in the public ordering nicotine salts and using it and injecting it and snorting it?
A. No.
Q. Have you seen nicotine available in other forms other than for things that you use on laboratory research?
A. Sure.
In fact, most people are aware now that nicotine is available in patches and gum, over the counters, no prescription, anybody can walk in and buy them. And, plus, I ordered some nicotine water

over the Internet.
Q. Nicotine water?
A. Right.
Q. Can you show us a bottle of that?
A. I've got a couple of bottles here.
MR. SCHNEIDER:
Let me ask you to pull up DDA-2038.
EXAMINATION BY MR. SCHNEIDER:
Q. Now, Doctor, tell us about what is this nicotine water?
A. It's just nicotine in water. It's a two-milligram, which is a 2 percent nicotine solution. And there was a -- there's a website nicotinewater.com. And I got a case of it.
Q. Now, is this some sort of a smoking-cessation device?
A. It could be used for that. I mean, I don't, again, know that anybody uses nicotine water for any purpose, but --
Q. Is it described on the bottle as to what it is?
A. It says on the bottle it's a dietary supplement.
Q. A dietary supplement?
A. Right, which would be like -- That's how they market caffeine drinks, for example. They don't control caffeine purchased because you can make Mountain Dew and Surge and other drinks that have a lot of caffeine in it.
Q. Now, have you heard any report or seen any reports in the literature or the newspaper or elsewhere of people in the public ordering nicotine

water, boiling it down, snorting it, injecting it, abusing it?
A. No, people don't use nicotine in any form as a drug of abuse. That's --
Q. Have you ever heard or seen anything like

cocaine water?
A. No.
Q. Or heroin water?
A. Well, those would be illegal.
Q. Or cocaine patches?
A. No.
Q. Or heroin patches?
A. No.
Q. Heroin gum?
A. No heroin gum.
Q. Cocaine gum?
A. No.
Q. And, yet, anyone in the public could have ordered this bottle of nicotine water you're talking about?
A. Right.
Q. And anyone could have ordered your bottle of nicotine that we saw that you showed us a moment ago?
A. Yeah, they can today order it. If they want to have nicotine and buy nicotine, they can order it. It's not controlled. It's not a controlled substance.
Q. All right. Now, are there guidelines in the United States put out by the National Advisory Council or drug abuse that relates to the differences between cocaine and, say, caffeine and

nicotine?
A. Yes, this has to do with when you are going to do experiments with drugs, whether -- what precautions you have to take using different drugs of abuse with experiments, with humans.
Q. And do those guidelines --
MR. SCHNEIDER:
Well, let's pull up, if we could, this is an exhibit, GK-100303. And let's pull it up for The Court and the witness and opposing counsel.
I don't believe there's an objection, but I want to be sure.
THE COURT:
No objection.
MR. SCHNEIDER:
All right. No objection.
Can we publish the first page?
And, Your Honor, we move into evidence GK-100303.
THE COURT:
You may publish it and it will be received in evidence.
EXAMINATION BY MR. SCHNEIDER:
Q. Now, Doctor, can you tell us what this first page is?
A. That's the cover letter to the advisory that I received as a drug researcher from the National Institutes of Drug Abuse, which -- And what follows then is the guidelines for using these drugs in subjects.
Q. And does this give you advice and guidance on

the precautions you should take in doing research concerning drugs?
A. Yes.
Q. And is there a reference in these guidelines to using cocaine and, say, nicotine?
A. Yes.
Q. Can you direct us there? Where is that in the document?
A. That's the fourth page. This is the cover letter, then there are four -- I think it's a five-page document.
MR. SCHNEIDER:
All right. Bert, can you take us there?
And can you highlight the sentence at the end of that first paragraph up there, I believe it is.
Is that right, Dr. Rowell?
THE WITNESS:
I don't think that's the page.
MR. SCHNEIDER:
All right.
THE WITNESS:
Let's see. Yes, that's the page.
MR. SCHNEIDER:
All right.
THE WITNESS:
It's the last -- the first paragraph, the last couple of sentences would be where it talks about specific drugs.
MR. SCHNEIDER:
If you could highlight that, Bert, pull that up and blow it up and highlight it.

EXAMINATION BY MR. SCHNEIDER:
Q. And, Doctor, that says "It should be remembered that a wide range of potentially abusable drugs may be the focus of drug administration research -- from caffeine and nicotine to cocaine and opiates"; correct?
A. Yes.
Q. And what conclusion, if any, do you draw from that language in the advisory guidelines?
A. Well, they're basically saying -- In fact, it says in the next sentence, "Depending upon the drug, exposure to these drugs have very different levels of risk for potential participants."
So, basically, what it's saying is the risk to become a nicotine abuser is about like cocaine. So you have -- you have research on a wide range. Once again, my focus is that dependence is not all or none. There's a range of dependence potential. Some have high, some have low. In my opinion, nicotine is very low; cocaine and amphetamine are very high.
Q. Now, Doctor, let me interrupt you.
A moment ago, I think you said the potential for being a nicotine abuser is about like cocaine. Is that what you meant?
A. No, no, I'm sorry. I meant caffeine, I

guess.
Q. Okay.
A. So here it says nicotine and caffeine at one end of the spectrum, basically, to cocaine and opiates, which would be heroin and morphine, at the other.

So, basically, this advisory is just telling researchers there is a different level of risk for potential participants when you use nicotine in drug research as compared to what you would have with, let's say, cocaine or heroin.
Q. All right. You can take that down.
I want to talk a little bit about withdrawal symptoms that are reported in the pharmacologic literature with respect to various drugs.
Have you studied during your career, Dr. Rowell, the various withdrawal symptoms reported, for example, with opiates and barbiturates versus caffeine and nicotine?
A. Yes. That's a critical part of drug dependence for many drugs.
Q. In terms of withdrawal symptoms reported with these substances, how does nicotine compare with drugs like cocaine, heroin, alcohol?
A. Nicotine has some withdrawal symptoms. It's a little bit difficult to measure that in humans because nicotine is not taken in pure form, as we just talked about, by human subjects. They don't abuse nicotine.
So you have to try to figure out what is a withdrawal from a behavior because there are behavioral withdrawal symptoms, too. Gamblers, for example.
But, you know, I'm willing to admit that pure nicotine would have some withdrawal symptoms, which would be irritability and restlessness and things. Then you compare that to drugs like the barbiturates or the opiates, like heroin and morphine, which, in

my estimation, have much more severe withdrawal symptoms.
Q. For example, withdrawal symptoms associated with, say, morphine and heroin, what kind of symptoms are those, what kind of withdrawal symptoms?
A. You get convulsions, you get diarrhea and delirium and confusion. And these drugs are intoxicating substances; whereas, in barbiturates, you could actually die from barbiturate withdrawal. Many of these withdrawal symptoms have to be treated medically, some don't, but they're still rather severe.
Q. And is nicotine an intoxicating substance?
A. No, nicotine is not intoxicating at all.
Q. Now, you mentioned that you could have withdrawal symptoms from or reported from gambling or other behaviors?
A. Yes.

Q. Could those -- If you stopped gambling, for example, what kind of withdrawal symptoms could you have?
A. Well, they're actually similar to what is categorized as nicotine withdrawal symptoms. And a lot of times with behavior withdrawal, they're more properly probably classified as abstinence syndrome because you're not undergoing a behavior rather than a withdrawal, which you think would be a drug.
But difficulty sleeping, people who are behaviorally dependent on certain behaviors, difficulty sleeping, irritability, you know, things like that. The same kinds of things that you get

with nicotine and, by the way, caffeine which, obviously, has some withdrawal symptoms as well for heavy caffeine coffee drinkers, for example.
Q. So if I'm used to having four or five cups of coffee a day and I stop doing that, I will have -- I could have some withdrawal symptoms?
A. Yes.
Q. Be irritated?
A. You're going to get a headache and you're going to be irritable and you're going to have difficulty concentrating.
Q. And suppose I'm someone that for years has, you know, come home, eaten a bag of Chee-tos, a big glass of milk, some Twinkies and I stop doing that, would I feel irritated?
A. Yeah, if you became -- I mean, people can probably become dependent on a lot of repetitive behaves. I would think that would be difficult to have people do that repetitively enough to have a behavioral dependence on those. But, certainly, there are behaviors that, repetitively engaged in, that if you stop, you get withdrawal symptoms.
For example, there's many exercisers and runners who, when they hurt theirselves and they can't exercise, they have clear abstinence syndrome effects. They're, you know, dependent, exercise dependent or chat room Internet dependent. I mean, there are all kinds of behavioral dependencies.
Q. Would you say that there's a sliding scale of withdrawal symptoms with respect to various drugs and chemicals?
A. Absolutely.

Q. And that cocaine and alcohol and heroin are on the high end, and that nicotine and caffeine and other substances are on the lower end?
A. Yes.
Once again, there's a gradation of effects of drugs. They can't all be classified as just, you know, dependent-producing. There's severe dependence, moderate and very mild dependence. And that relates to the amount of withdrawal that you get.
Q. All right. Now, Doctor, I want to talk about a topic that's called up-regulation. Do you know

what up-regulation refers to?
A. Yes.
Q. What is up-regulation?
A. Up-regulation is a phenomenon that happens on most of these receptors. We had these little receptors that were up at the synapse. And anytime drugs are given for long periods of time, the body tries to counteract that because it wants to bring itself back into balance.

Normally, up-regulation is seen when you give a drug that blocks a receptor. The body says I'm not getting enough stimulation of this receptor because I put in a blocker, so they up-regulate. It means that you end up with an increased number of those little green receptors that we had on that picture. That would be up-regulation.

It's commonly seen with patients that take what are called beta blockers for high blood pressure, things like that.

MR. SCHNEIDER:

Let's bring back up DDA-2041.

EXAMINATION BY MR. SCHNEIDER:

Q. Now, Doctor, we talked earlier that the green blocks on the downstream nerve, those are receptors; correct?
A. Correct.
Q. And when we talk about up-regulation, are we talking about that it causes more of those receptors to exist?
A. Yes, after long -- well, not even long term. A week, let's say, of using a drug for that period of time, you will be able to measure receptor up-regulation.
Q. And does nicotine relate to an increase in the number of receptors in the body?
A. It has been discovered that nicotine produces up-regulation. First, it was discovered as usual in animal studies in 1983. And then later on -- These are brain receptors. So you can't, once again, measure these in a living human being.

But in postmortem studies of smokers, after they've been killed in a car accident or something, it's been determined that smokers have also an increased number of these nicotinic/acetylcholine receptors compared to nonsmokers. So, yes, there is an up-regulation.
Q. A question about nicotinic receptors a moment. You said that when these receptors were first discovered back in the 1800s, they were called nicotinic receptors because they used nicotine to discover them?
A. Yes.

And part of that was because no one knew any neurotransmitters back then. Acetylcholine had not been discovered, which is what our body actually uses to work on those receptors. So they knew there was something there that was producing the response

to nicotine, but it turns out these are really acetylcholine receptors. But they're called nicotinic receptors now.
Q. All right. And the term given to them was "nicotinic receptors." And that was whether a person smokes or not, we have nicotinic receptors in our body?
A. Yes, all the time.
Q. Even if a person never smoked?
A. Right.
Q. Those receptors in our body scientifically are called nicotinic receptors?
A. That's right. I mean, that's where the acetylcholine neurotransmitter, those nerves that use acetylcholine work on nicotinic receptors.
Q. Okay. And I think we touched on this a moment -- a little while ago. But we see that nicotine there in the synapse. And I think we talked about how that got there. It's by taking a puff of smoke; correct?
A. Right.
Q. It goes into my lungs, then through the bloodstream, into the brain, and ultimately into the nerves?
A. Right.
It actually goes from the lung back to the heart, because you have two chamber sides to the

heart, and then it's just distributed to wherever blood goes from the heart. At rest, it's somewhere around a fifth, maybe 20 percent of the blood goes to the brain, 80 percent goes somewhere else. So 80 percent of the nicotine is going other places and about 20 percent to the brain.
Q. All right. And you say that nicotine can cause receptors, nicotinic receptors, to increase?
A. Right, over -- if you're exposed to nicotine for four to seven days, the receptors gradually -- the number of receptors actually increase.
Q. Now, for all smokers, let's suppose -- let's assume, Doctor, for a moment, that the class in this case consists of persons in Louisiana who are either a current or former smoker as of 1996, okay?
A. Okay.
Q. Would everyone in that class have an equal degree of up-regulation?
A. Not at all.
Q. Does up-regulation vary from individual to individual?
A. Well, you mentioned, I think, former smokers.
Q. Yes.
A. And former smokers don't have any receptor up-regulation. Because whereas the receptors up-regulate in about a week, they come back to normal in about a week after you stop taking nicotine.
Q. All right. So after I've stopped smoking, the receptors come back down to normal?
A. Right.
Former smokers -- and these are, again,

postmortem studies -- have no increase in receptors over other people. In animal studies where you can actually measure this every single day, you can measure receptor numbers in their brain, it's been determined that they return to normal over about a week.
Q. All right. But let's talk about current smokers. People who are currently smoking, they might have an up-regulation of their receptors; correct?
A. They might.
Q. Do you have to smoke a certain amount in order for there to be an up-regulation of receptors?
A. Well, I'm sure that's true. Probably like everything else, there's kind of a distribution of effects. People are all different. And some people would have dramatic up-regulation, some people would have lower up-regulation. That's seen in animals, too. That's why you report an average number. Plus, some kind of a standard error or standard deviation from the mean.
Q. So this would vary from individual to individual?
A. Certainly.
Q. Could it also be affected by individual genetics?
A. Yes.
Q. In terms of the effect of up-regulation, compare that to cocaine, does cocaine cause an up-regulation of receptors?
A. No.
Q. What does it cause?

A. Cocaine and most of the drugs that are thought of as abusable through the dopamine system cause a down-regulation in receptors. Because the system is being overstimulated. And as I mentioned, the body doesn't like that, it wants to return to normal. But you're still taking the cocaine, for example. So the way the body compensates for the overstimulation is to decrease the number of receptors to return back to normal.
Q. Well, Doctor, let me ask you. Is there a basic concept in pharmacology that basically says that the amount of a drug plus the amount of receptors equals a given effect?
A. Yes.
Q. And so if that is a formula that I have here in the air, amount of the drug, amount of receptors equals effect --
A. Right. That's in every pharmacology textbook, the D plus R, drug plus receptor, equals effect.
Q. All right. Well, under that formula that we have floating here in the air for us, if I increase the amount of receptors, does that mean I need less of the drug to get the effect?
A. Right, because D plus R gives you the same effect. So R, receptors, go up. If you don't do

anything else, you get more effect. And the only way to bring that back is less D.
Q. All right. So back to our formula, the amount of drug plus the amount of receptors equals effect. So if I increase the amount of receptors, I'll need less of the drug to get the effect?

A. Yes.
Q. Okay. Now, with cocaine, you say that causes a down-regulation of receptors?
A. Yes.
Q. So under our formula, amount of drug plus amount of receptors equals effect, cocaine causes the receptors to go down, you need more of the drug to get the effect?
A. Yes.
In fact, that's what tolerance is. You become tolerant, so you have to take more of the drug to get back to where you were because you have less receptors. That's drug tolerance.
Q. And so it is down-regulation that would be associated with the need for more and more and more drug?
A. Right.
Q. Whereas, up-regulation would technically be associated with the need for less drug?
A. Yes.
And that's known for many, many drugs that are commonly used for other things, you know, heart medications and angina medications and things.
Q. When I was first learning about that, it was sort of hard to think that if you have more receptors, it seemed like maybe you'd need more drugs. But you're saying the formula is to the opposite effect?
A. Right.
If you have more receptors, you would actually be sensitized to having a little bit of drug in there because you've got a lot more

receptors to respond, so you could get the effect with less drug.
Q. Let's take an analogy.
If we took this room and we filled it with glass tumblers, let's say each glass tumbler or glass is a receptor, okay?
A. Okay.
Q. And let's suppose I need to get a drop of water in four or five of those glasses in order to have an effect, whatever the effect might be.
A. Okay.
Q. If I open the door in this room and I've got the room filled with these little glasses, spray a hose in here, all I need to do is get a little bit of water and I'm pretty certain to hit a few receptors and get my effect; right?
A. If you have a lot of glasses, you're probably going to get the effect pretty quickly.
Q. So I've got a lot of receptors in the room, I

need less drug?
A. Right.
Q. Now, if I take this room and I take all of the glasses out of here and I leave three or four in corners of the room, I have less receptors now?
A. Right.
Q. And now when I put my hose of drug in here and I start spraying it, I'm going to need to spray a lot more to try to hit these receptors. Is that the basic concept we're talking about here?
A. I guess that's a good way to think about it. If you have fewer of these receptors, you need to put in more drug to bring you back to normal.

Q. All right.
A. Which is, again, what I said happens with tolerance. And it also has to do with withdrawal as well.
Q. And this up-regulation that we talked about, you said that once you stop smoking or stop smoking a certain amount, your receptors will go back to normal?
A. Right.
Q. So there's not a permanent change in the brain?
A. No, not on those receptors, no.
Q. And if I have additional receptors, will I know that? Will I as a human being know I have extra receptors?
A. No.
Q. It's not -- It won't be manifest to me?
A. Yeah, you won't -- you won't know about it.
Q. Can caffeine cause an up-regulation in the number of adenosine receptors?
A. Yes.
Q. And do those also go away or go back to normal when someone stops drinking coffee?
A. Yes.
Q. Now, I want to talk about memory a little bit. When we're little children, we learn to tie our shoe. Does that imprint a memory in our brain?
A. Well, yes. I mean, your brain changes in some way as a result of learning anything.
Q. All right. And if for the next 20 years I wander around wearing sandals or loafers and then 20 years later I come upon wearing a pair of shoes that

have laces, my brain will have a memory of how to tie that shoe?
A. Right. You've learned it. It's riding a bicycle is what people have the analogy to.
Q. All right. And that's a memory? That's not an injury to my brain? It's a memory?
A. Right. It's not actually so much as a memory as -- because you might, you know, you don't really think about that you're remembering it. But it's a change that happens in the brain which allows you to be able to do things more easily the next time. Actually, more synapses are formed which makes the

electrical current go easier through that system.
Q. All right.
A. So there are physical changes in the brain, right.
Q. Let's talk about spinach. You know, when you're a, again, when you're a little kid --
A. Where are we going with this?
Q. I'm not quite sure myself.
When you're a little child, you eat some spinach and you don't like it, all right? Assume that.
A. Okay.
Q. Twenty years later, you've grown up a little bit, you go to a nice restaurant, you have spinach sauteed nicely, some garlic, you try it, it's delicious, does that imprint a memory in your brain or sense recollection of that experience?
A. Yes. I mean, really, any experience, all experiences you go through -- and, of course, more traumatic ones cause more greater effects -- but all

these experiences change the brain in subtle ways as a result of your experiences in your learning and your memories.
Q. But it's a memory or a sense impression, not an injury to your brain; correct?
A. No, it's not an injury.
Q. And if for 20 years you don't eat that spinach again, and you come upon a plate of this piping hot spinach, and your brain remembers it, is that the sense memory we're talking about?
A. Yes.
Q. Now, with respect to a smoker who might smoke in their twenties and enjoy the sensation and feeling of smoking, will that create a sense memory of that smoking behavior?
A. Certainly.
Q. And if they come upon a cigarette 20 years later, having quit 20 years later, and they have a memory that -- the sense that smoking might be enjoyable, is that attributable to that sense memory we're talking about?
A. Yes.
Q. Now, the last couple of topics I want to cover with you relate to smoking behavior and the tobacco company documents.
We talked at the beginning of an effort to try to figure out to what extent is nicotine driving people to smoke compared to the other things about smoking behavior; correct?
A. Yes.
Q. I guess you could take a cigarette and take the nicotine out of it and smoke it; is that

possible?
A. You could.
Q. And if I smoke that cigarette, I would get a certain sensation in my mouth, a taste sensation in my mouth; correct?

A. Right.
Q. I'd get a sensation from inhaling the smoke; correct?
A. Yes.
Q. I'd get a sensation from blowing out the smoke?
A. Yes.
Q. I'd get a sensation, I guess, from whatever other chemicals that are in the smoke in my body; correct?
A. Right.
Q. We're trying to separate that out from what the effect would be of the nicotine in the cigarette.
A. Right.
Q. Now, have there been studies published in the pharmacological field that try to do just that? Separate that out and see what's driving smoking?
A. Yes.
Q. And have you reviewed those studies?
A. Yes, I have.
Q. And can you present to us the results of one of those studies here today, try to get a grasp on this concept?
A. Right.
MR. SCHNEIDER:
And let me put up a graphic which is

DDA-2053.
EXAMINATION BY MR. SCHNEIDER:
Q. Now, Doctor, down at the bottom of this DDA-2053, there's a citation to a study by J. E. Rose; correct?
A. Right.
Q. Who is Dr. Rose? Is he a doctor?
A. Yes, he is.
Q. And what was his -- who is he and what was he doing in this study?
A. This is Jed Rose. He's the Director of the Nicotine Research Center at Duke University. And he in this study attempted to do what not too many people have done, which is to separate out the nicotine, the pure nicotine effect of smoking from the act or the behavior of smoking.
So how the study was conducted, he took smokers and deprived them of cigarette smoking overnight and then brought them into the clinic. By the way, he had measured their nicotine -- the nicotine that they get from smoking in a previous study on that subject. So he knew exactly when they smoked, how much nicotine goes into the blood at what time. He pulsed it in.
So the next day, these subjects -- and there were a lot of them -- came into the laboratory. And they were given an I.V. cannula, the little needle in their vein, hooked up to a pump. And that pump would administer either saline or -- over here (indicating), pulsed I.V. saline -- or pulsed I.V. nicotine, which mimicked the amount of nicotine that they got when they smoked a cigarette. So it pulsed

it in as if they were smoking a cigarette.
So they have a little cannula. And these people --
Q. I'm sorry. When you say "cannula," that's like an I.V.?
A. A little I.V. needle.
Q. Okay.
A. And these individuals, as is done in all good drug studies, is blind. They don't know whether what's coming into their vein is going to be the saline or the nicotine. They just know that the pump went off and something came into their vein.
So then the subjects were asked to rate -- This is one of the, by the way, number of charts that this publication had. This one happens to be "Satisfaction," but there were other ones that were very similar.
They were asked to rate on a scale how satisfying whatever happened to them felt. It's another one of these kind of feel-good things. So here these subjects are doing nothing. They're sitting in a chair, and they're getting either pulsed saline in the vein or pulsed nicotine as if they were getting it from a smoke. So it's the pure nicotine effect.
Q. And they don't know which one they're getting?
A. No.
Q. And they're being asked how satisfying is that?
A. Right.
And they might be getting -- They don't --

They might think they're getting nicotine or maybe not.
Q. And the green is saline or water?
A. Saline.
Q. And the yellow is nicotine?
A. That's the pure nicotine coming in.
Q. An injection of pure nicotine? It's not smoking?
A. Right, it's not smoking. They're not smoking.
Q. And they're reporting them to be close, but nicotine they like slightly better than water?
A. Right.
Q. All right. Tell us about the next two columns.
A. Okay. The other subjects were -- had the intravenous cannula, the intravenous tube going in, hooked up to the same pump. They also got either saline or a nicotine injection.
But these individuals were smoking, they were going through the behavior of smoking a cigarette that didn't have any nicotine in the cigarette at all. So it was a --
Q. Did they know that?
A. No.
In this study -- and Dr. Rose tries to do a

lot of these masking studies -- nicotine imparts a lot of sensory effects to cigarette smoking. Individuals can usually tell, if you give them a non-nicotine cigarette, they report they're pretty lousy tasting. They've tried to market low nicotine, really low-nicotine cigarettes before, and

they don't do very well on the market.

This study tried to mask that effect by putting in capsaicin, which is kind of a peppery compound, into the cigarettes to try to let them get the impact, what's called the impact, which is the throat effect, scratch, from these cigarettes.

Q. All right. And so in the middle column there, on the green column, someone was smoking a denicotinized cigarette and getting water?

A. Right.

Q. In the other column, somebody was smoking a denicotinized cigarette and getting the stream of nicotine?

A. Pulsed nicotine.

Q. And they were asked how satisfying it was. They rated the denic cigarette with nicotine slightly better?

A. Right.

So this yellow bar should be kind of like your regular cigarette. You're smoking and you're getting the nicotine as if you were smoking, but it's coming in through the intravenous cannula.

Q. And the last bar on this chart, Doctor, represents what?

A. That's the usual brand they were then allowed to rate. If they were a Marlboro smoker or whatever, they rated their usual brand. In this case, they're getting the nicotine from -- they have a pulsed injection but it's saline. They're getting their nicotine from their cigarette.

Q. All right. Now, if I wanted to take out all the stuff on this chart and just separate it down,

show me the people who had just pure nicotine coming into them versus someone who is smoking a denicotinized cigarette without any nicotine.

A. Okay.

Q. Can I -- Is there a way to take all the columns off this chart and just have those two columns?

A. Yes. I prepared that chart because the bars I think are important to focus in on on these studies, this and others, is to try to separate out what you get from nicotine compared to what you get from pure behaviors, just the act of smoking, the manipulation, the drawing in, the puffing, everything else, which is this bar. So that's the next bar.

MR. SCHNEIDER:
All right. Let's take a look at 2054.

EXAMINATION BY MR. SCHNEIDER:

Q. Now, Doctor, you've taken out all the other

bars. And what we show is the yellow bar there are people who are just getting pure nicotine with no smoking?
A. There's no behavior. That's the pure nicotine effect.
Q. And then the other bar is they're not getting any nicotine at all?
A. No nicotine.
Q. And they're smoking a denicotinized cigarette?
A. They're getting no nicotine, but they're going through all of the behavioral aspects of smoking a cigarette.

Q. And you're saying which one do you like better, in effect?
A. Right.
Q. And the result is that they're reporting more satisfaction with just smoking even without nicotine than they do over pure nicotine?
A. Right.
Q. And is the bottom line of this, Doctor, if you go back to 2053 a moment, is the bottom line of this is that these smokers stated they preferred a cigarette with nicotine over a cigarette without nicotine but they greatly preferred smoking over pure nicotine?
A. Right.
The bottom line to me is that when these individuals who are overnight abstinent, they're cigarette smokers, what they want to do is smoke. They want to go through the act of smoking. And that's what they find satisfying in this situation.
Giving somebody who wants to smoke, they're craving the smoke, nicotine does not substitute, pure nicotine does not substitute for that as well as just the behavior of smoking.
Q. All right. So in this particular study, people who smoked denicotinized cigarettes reported to be more satisfied than getting a pure injection of nicotine?
A. Right. And these other charts in here and, actually, other studies have shown similar things.
Q. All right. And what conclusions, if any, do you draw from that, Doctor?
A. Well, my conclusion is -- and I've had this

conclusion for a long time based on what I know about how reinforcing or lack thereof nicotine is -- is that cigarette smoking is very much a behavioral dependence reinforced by a little bit of drug effect.
But that it is not a drug addiction to a drug like cocaine or heroin; that it is behavioral. Because of the very repetitive nature of smoking, the ritualistic nature of smoking, there are a lot of behavioral aspects to smoking which make it -- You have to understand -- You have to appreciate the behavioral aspects of smoking and not just say

because it's got a drug in it that nobody uses by itself.
Q. All right. Now, Dr. Rowell, let me change topics and we'll conclude. This will take us through the lunch break.
If you could pull down 2053.
Doctor, we talked about the fact that you were given copies of company documents; correct?
A. Yes.
Q. And these were company documents that you understood had been selected by plaintiffs' counsel; correct?
A. Right.
Q. And you understood that these documents were being pointed at by plaintiffs' counsel as showing new breakthroughs with respect to nicotine; correct?
A. Well, they were -- they were identified by plaintiffs as containing some information which would be important for something.
Q. All right. Important with respect to

nicotine in concepts of addiction?
A. Yes. I mean, whatever they thought they were important for, right.
Q. And did you review those documents that had been selected by plaintiffs in various cases to determine whether they contain any new scientific breakthrough with respect to nicotine and addiction that had not been previously reported on in the published literature?
A. Right.
The university scientists, government scientists, federal laboratory scientists, foundation scientists have done a lot of really good research. And I didn't see any scientific studies that were ahead of what was already being done by drug researchers outside.
Q. Did you see documents, Doctor, in which persons inside tobacco companies would describe smoking as an addiction?
A. Sure.
Q. Did you see documents saying that the cigarette companies were in the business of selling an addictive drug?
A. Yes.
Q. Did any of those studies -- Did any of those documents, in your judgment, contribute a new scientific breakthrough that was not published in the published literature?
A. No, because there was no foundation for those statements. Those statements have been made in the popular press since the 1930s. And there were no science to back it up, so -- And a lot of these

statements were made by marketing people and attorneys and they weren't even scientists.
So I read a lot of those kinds of statements in the documents, that they were using the term "addiction" and things like that. We know this.

But they knew it on the basis of the fact that they were keeping up with the published literature and it had been reported in the press, not because they did any science in their laboratories to show anything new that was not already known.

I mean, I have seen no studies or data or charts or graphs which preceded and allowed a great increase in knowledge that the tobacco companies actually did in their own laboratories and kept in their documents.

Q. Dr. Rowell, based on all of your training, your education, the research and experience that you have done and have, in your opinion, is the presence of nicotine in tobacco and in cigarettes capable of preventing a person from quitting smoking, if they want to?

A. No. I think nicotine contributes to cigarette smoking behavior, but it does not -- it is weak enough, it does not prevent an individual from stopping that behavioral dependency.

MR. SCHNEIDER:

Thank you, Dr. Rowell. I appreciate it.

Your Honor, we're at the lunch break and that's my last question.

THE COURT:

We'll recess for lunch until 1:30 by the wall clock.

(Whereupon the jury is excused at this time.)

THE COURT:

Let the record reflect the jury has left the courtroom.

Anything for the record by plaintiffs' counsel?

MR. BRUNO:

No, Judge.

MR. RUSS HERMAN:

No.

THE COURT:

Defense counsel?

MR. WITTMANN:

No, Your Honor.

THE COURT:

This is a reminder again. Tomorrow we start at 1:00 p.m. rather than 9:30 just so nobody will forget that. We'll recess until 1:30.

(Whereupon the proceedings were adjourned at 12:00 o'clock noon.)

* * * * *

REPORTER'S CERTIFICATE

I, CHERYL FOURNET HUFFMAN, Registered Merit Reporter, in and for the State of Louisiana, as the officer before whom this testimony was taken, do hereby certify that this testimony was reported by me in the stenotype reporting method, was prepared and transcribed by me or under my personal direction and supervision, and is a true and correct transcript to the best of my ability and understanding; that I am not related to counsel or to the parties herein, nor am I otherwise interested in the outcome of this matter.

_____

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